



National Institutes
of Health



Helping to End Addition Long-term (HEAL) Initiative

Developing Medical Devices to Treat Pain

webinar will start at 3:00pm EDT

12/13/2018



National Institute of Biomedical Imaging
and Bioengineering



National Institutes of Health
Office of Strategic Coordination - The Common Fund



National Institute of
Neurological Disorders
and Stroke

Housekeeping

- If you have trouble connecting to audio via computer, use a telephone: 1-650-479-3208 , , 626 928 973 #
- *Please mute your phone until the Q&A portion of the webinar*

Housekeeping

- This webinar will be repeated on December 20
- Slides will be posted
- Frequently asked questions will be answered
- If your question is not answered today,
*please check the website or
please contact us by email*

https://www.nibib.nih.gov/devices_for_pain

Presenters



[Michael Wolfson](#)
NIBIB
Device development



[Michael Oshinsky](#)
NINDS
HEAL Initiative



[Gene Civillico](#)
OSC/Common Fund
Device-able targets



[Kari Ashmont](#)
NINDS
First-in-human

Outline

- Introduction to the NIH [HEAL Initiative](#)
- 1. [Anatomical and Functional Mapping of Pain-Related Visceral Organ Neural Circuitry](#) (U01 CT Optional)
- 2. [Translational Development of Devices to Treat Pain](#) (U18 CT Not Allowed)
- 3. [Translational Devices to Treat Pain](#) (UG3/UH3 CT Optional)
- 4. [Translational Devices to Treat Pain](#) (U44 CT Optional)
- 5. [Clinical Devices to Treat Pain](#) (UH3 CT Optional)
- Public-private partnership
- Interactive Q&A

National Institutes of Health

There are 27 different Institutes and Centers (ICs), 24 of which award grants



Disclaimer:

Individual NIH Institutes and Centers have different programs, guidelines and policies.

ALWAYS CONTACT PROGRAM STAFF WELL IN ADVANCE OF APPLYING FOR A GRANT

NIH HEAL (Helping to End Addiction Long Term) Initiative

The Unmet Medical Need for Non-Addictive Pain Therapeutics

- >25 million Americans suffer from chronic pain
- Over-reliance on opioid treatments due to lack of alternatives

HEAL (Helping to End Addiction Long-term)

- An aggressive, trans-agency effort to speed solutions to stem the national opioid public health crisis



Development of New Non-Addictive Treatments for Pain

- Discover and validate neural targets
- Develop technology to diagnose or treat pain
- Demonstrate diagnosis or treatment with first-in-human study

<https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative>

NIH Helping to End Addiction Long-term (HEAL) Initiative: Pain Research Priorities

Enhance Pain Management

- Understand the biological underpinnings of chronic pain
- Accelerate the discovery and pre-clinical development of non-addictive pain treatments
- Advance new non-addictive pain treatments through the clinical pipeline
- Inform best practices for effective pain management while minimizing risk of addiction



Read about the 2018 research plan:

www.nih.gov/heal-initiative

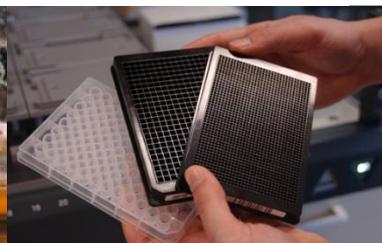
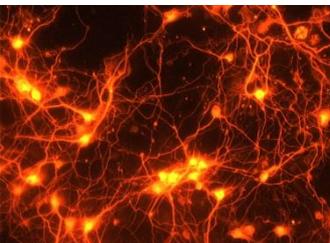
JAMA June 12, 2018

Opinion

VIEWPOINT

Helping to End Addiction Over the Long-term
The Research Plan for the NIH HEAL Initiative

Collins, Koroshetz, Volkow; JAMA, 2018



Overview of Proposed HEAL Programs for Pain

Discovery

Preclinical Development

Clinical Trials

Acute to Chronic Pain Signatures

Discover and Validate Novel Targets for Safe and Effective Pain Treatment

Preclinical Screening Platforms + Optimization of Non-addictive Therapies to Treat Pain

Translating Discoveries Into Effective Stimulation Devices For Pain Treatment

Discovery and Validation of Biomarkers, Biomarker Signatures, and Endpoints for Pain Indications

Data and Asset Sharing Partnership

Early Phase Pain Investigation Clinical Network

Back Pain Research Consortium

Pain Effectiveness Research Trials + Network

Pragmatic and Implementation Studies for the Management of Pain

This webinar

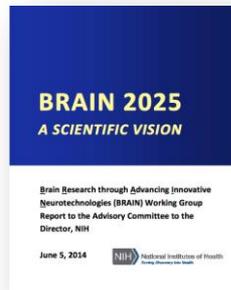


Medical Devices within HEAL

- This webinar covers FOAs that support devices to target the nervous system to provide therapeutic, rehabilitative, or diagnostic capability
- Other FOAs support developing devices to treat specific kinds of pain
 - [NIAMS Back Pain Consortium \(BACPAC\)](#)
- Other FOAs support developing devices to address opioid abuse, withdrawal, and addiction
 - <https://www.drugabuse.gov/drugs-abuse/opioids/nidas-role-in-nih-heal-initiative>
- Other FOAs support developing tissue chip devices
 - <https://ncats.nih.gov/heal>
- Other FOAs support developing and validating new biomarkers
 - <https://www.ninds.nih.gov/Current-Research/Focus-Tools-Topics/Biomarkers>

HEAL – Translating BRAIN/SPARC/HEAL Discoveries into Effective Stimulation Devices for Pain Treatment

Brain
Research through
Advancing
Innovative
Neurotechnologies



Stimulating
Peripheral
Activity to
Relieve
Conditions



The overall goal of this initiative is to translate diagnostic and therapeutic devices into humans to address the opioid epidemic through the development of non-addictive therapies that improve patient outcomes and decrease or eliminate the need to prescribe opioids.

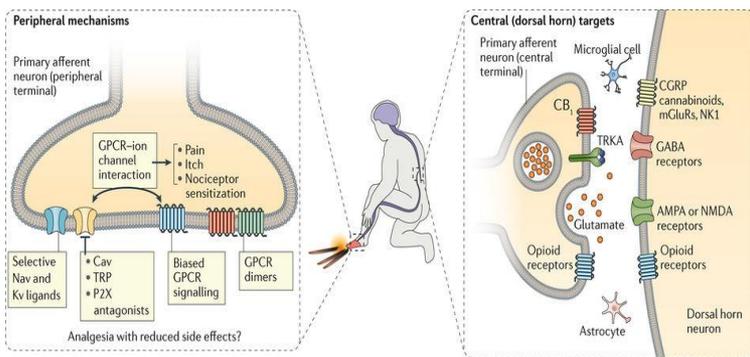
➤ Goals

- Leverage ongoing mapping / target discovery activities in BRAIN, SPARC, and other HEAL Initiatives
- Expand Public Private Partnership efforts in SPARC & BRAIN to engage medical device industry to explore repurposing devices for new indications

[NOT-NS-18-008](#): BRAIN Initiative: Notice of Support for Research on the Fundamental Neurobiology of Pain Processing

HEAL - Discover and Validate Novel Targets for Safe and Effective Pain Treatment

To promote the basic science discovery and validation of targets for the treatment of pain that can be used to develop treatments that have minimal side effects and little to no abuse/addiction liability



Nat Rev Drug Discov. 2017 Aug;16(8):545-564.

[RFA-NS-18-043](#) – R01

[RFA-NS-18-042](#) – R21

[NOT-NS-18-073](#) – Administrative Supplements

Basic biology target discovery projects

- Encourage collaboration from other fields
- Designed to reveal novel targets for small molecules, natural products, biologics, devices
- Devices: discovery of new sites for stimulation or electrophysiological signatures
- Open to all pain systems in CNS or periphery

Previously identified targets

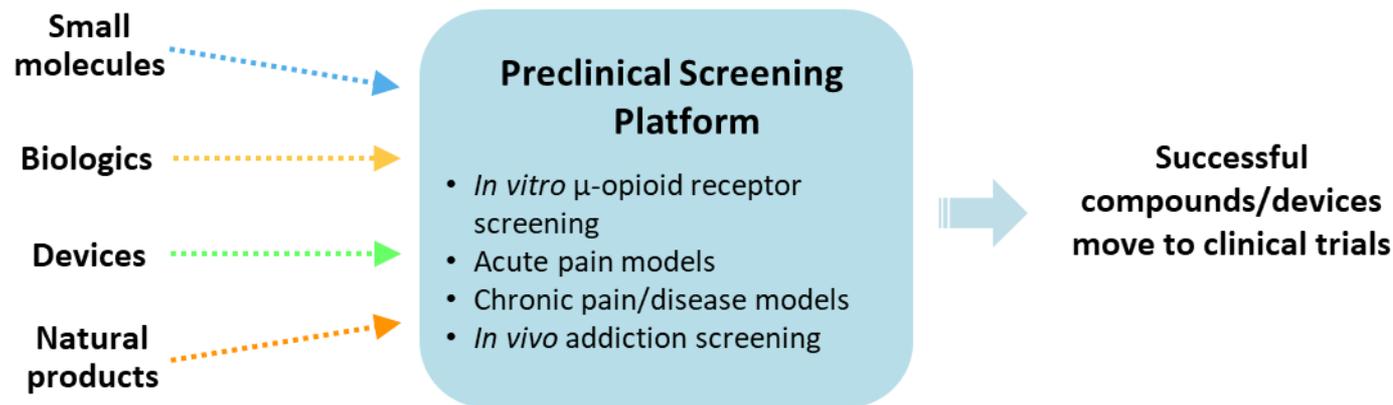
Pain target validation

- Novel *in vitro/ex vivo* assays
- Animal model systems development
- Multidisciplinary tools
- Multisite validation; robustness; reproducibility
- Validation of pharmacodynamic and predictive biomarkers

HEAL - Preclinical Screening Platform for Pain (PSPP)

Will establish a one-stop preclinical testing platform that promotes the testing and characterization of non-addictive modalities for the treatment of pain

- Incentivize academia & industry to accelerate discovery of non-addictive, effective therapies
- Develop or refine animal models of pain conditions-available to research community
- Generate high quality data to support partnerships, translational programs
- Provide access to research community



**2018: Work will start through the University of Utah
Epilepsy Therapy Screening Program**

2019: A new openly-competed contract will be awarded

Big Picture

Target finding and development

HEAL: SPARC:
Mapping Pain U01
(Common Fund)

HEAL: Target
Discovery and
Validation

HEAL: PPSP

Parent R01

Build new capabilities

BRAIN: PPP
SPARC: PPP

HEAL: Device
Development U18
(NIBIB)

BRAIN:
Tech development
U01/UG3/UH3

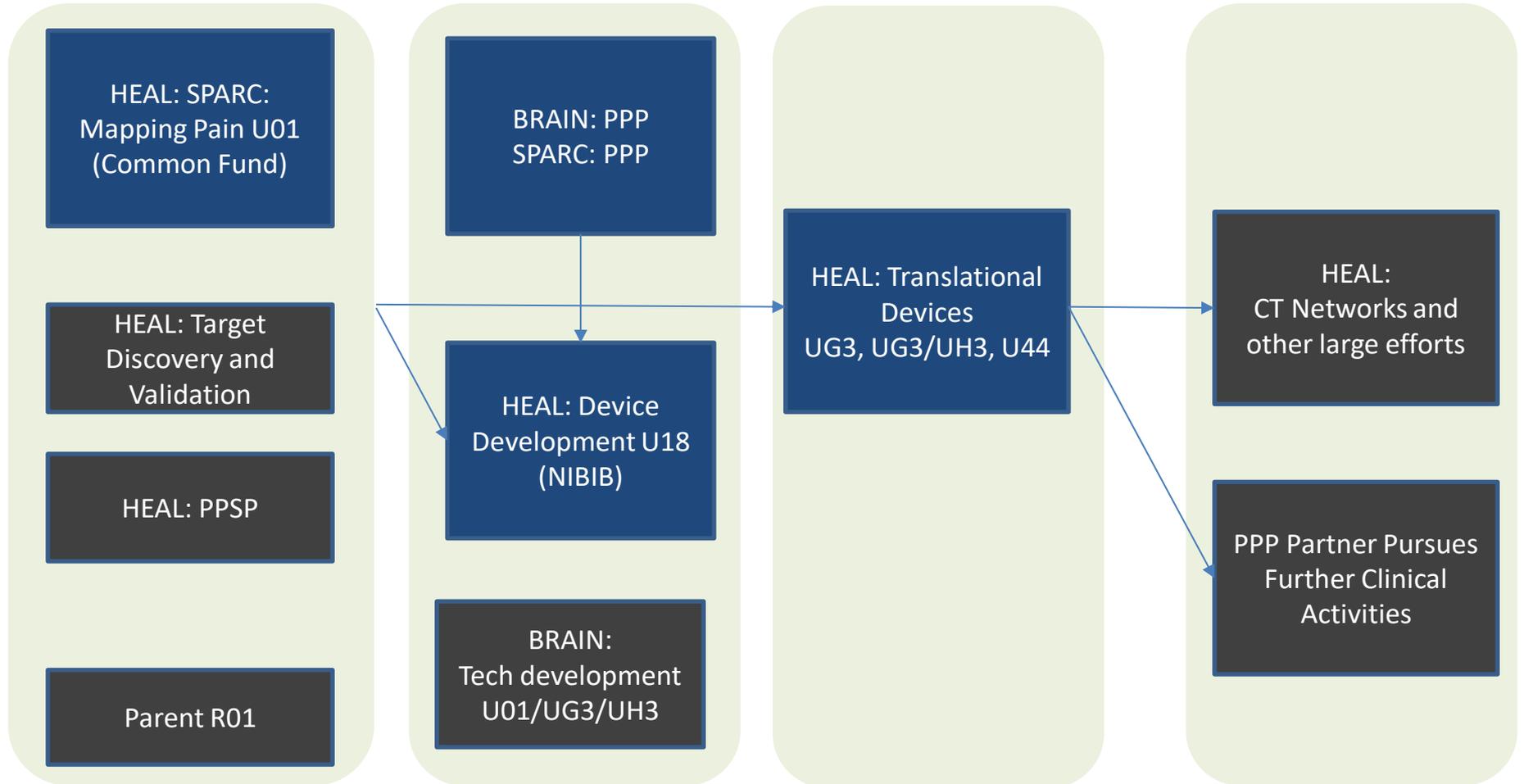
First in human with new capabilities

HEAL: Translational
Devices
UG3, UG3/UH3, U44

Translation

HEAL:
CT Networks and
other large efforts

PPP Partner Pursues
Further Clinical
Activities





SPARC Program (OD/Common Fund)

- **Opportunity:** Neuromodulation of end-organ function holds promise in treating many diseases/conditions.
- **Challenge:** The mechanisms of action for neuromodulation therapies remain poorly understood.

Provide a scientific foundation, e.g. anatomical and functional maps of the innervation of major organs, that enables better understanding of the neural control of organ function, **spurring development of the next-generation of therapeutic closed-loop neuromodulation devices.**

Stimulating Peripheral Activity to Relieve Conditions



Mechanism	Responsivity	Duration	Program budget	Anticipated awards in FY19	Receipt Date
U01	Any neural pathway that either includes or processes information from visceral afferents, up to the level of the brainstem	≤ 3 Yrs	Rarely exceed \$500k direct cost per year	\$5M; 8-10 awards	February 8

Foreign organizations **are not** eligible, but foreign components **are**

Awardees will be members of SPARC and HEAL consortia



Goals

- Anatomical tracing and functional probing of neural pathways processing visceral afferent information from internal organs
- **Clinical Optional** To enable Basic Experimental Studies in Humans (BESH)
- Generate future targets for study of device-based pain interventions



Responsive

- Animal models are responsive if relevance to humans is justified
- Project deliverables specified in terms of the sharing and annotation of particular types of data
- Support technology development as necessary for high-resolution circuit mapping
- Forward-looking data sharing and management plans; required participation in the SPARC Data and Resource Center

Not Responsive

- Develop or validate diagnostic procedures, rehabilitation strategies, small molecules, or biologics
- Primary objective is to test clinical hypotheses, efficacy, or effectiveness
- See "Neural Circuit Scope" in FOA: no sensory structures of the head or named voluntary muscles

Development of Devices to Treat Pain

Mechanism	Maturity	Duration	Budget	Anticipated awards in FY19	Receipt Dates
U18	Known mechanism	≤ 3 Yrs	Rarely exceed \$500k direct cost per year	\$3M; 5-10 awards	March 22 June 20 October 22 <i>more in 2020</i>

Foreign organizations **are** eligible

Human subjects research not anticipated

Development of Devices to Treat Pain

Goals

- Develop safe, effective, and non-addictive device-based technologies and approaches to treat pain via focal diagnosis, rehabilitation, or therapy
- Use mechanistic knowledge about the anatomy and physiology of central, spinal, and peripheral pain pathways to inform device design
- Facilitate the translation of new devices up to the stage of readiness for first in human (FIH) clinical trials

Entry Criteria

- Rigorous mechanistic biological rationale must be known and used to justify the anatomical target
- Early stage technologies will be considered, with a research plan and supporting data showing that clinical testing is likely within five years

Development of Devices to Treat Pain

Responsive

- Use state-of-the-art design practices to develop preclinical technology to the point of clinical testing
- Justify the anatomical target, and provide supporting data on the mechanism of the anticipated treatment
- Justify that the device will focally interact with the anatomical target
- Justify the specific pain condition(s) and population(s) to be addressed
- Use an existing animal model for the specific pain indication

Not Responsive

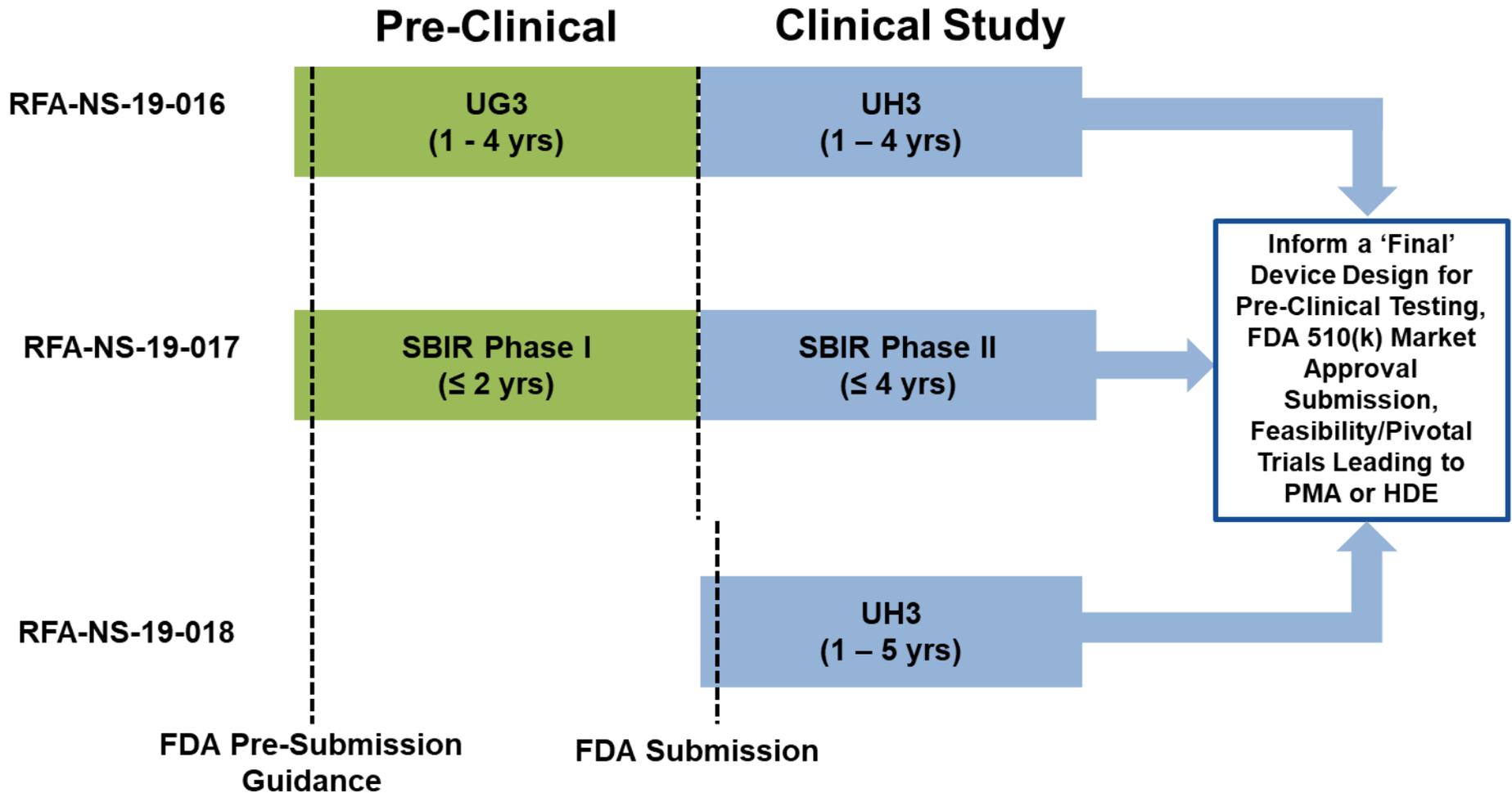
- The primary objective is to study scientific or clinical hypotheses, efficacy, or effectiveness
- The project does not conclude with clear path to human use
- The basis for the device's functionality is rooted in phenomenology or purely empirically determined measurements

Translational Devices to Treat Pain (TDTP)

Mechanism	Maturity	Duration	Budget	Anticipated awards in FY19	Receipt Dates
UG3/UH3	Known target; demonstrated <i>in vivo</i>	UG3: 1-4 Yrs UH3: 1-4 Yrs Total: ≤5 Yrs	No limit, but must reflect actual need	\$4M; 3-6 awards	Jan 9, 2019 Mar 22, 2019 Jun 21, 2019 Oct 21, 2019 Feb 21, 2020 Jun 22, 2020 Oct 21, 2020 Feb 21, 2021
U44	Known target; demonstrated <i>in vivo</i>	Phase I: 1-2 Yrs Phase II: 1-4 Yrs Total: ≤5 Yrs	Phase I: Rarely >\$1M in total cost per year Phase II: Rarely >\$1.5M in total costs per year	\$6M; 4-8 awards	
UH3	Known target; ready for HSR	≤5 Yrs	No limit, but must reflect actual need	\$3M; 3-4 awards	

Foreign organizations **are not** eligible

TDTP Phases



Studies lead to an Investigation Device Exemption (IDE) for a small clinical trial
or
Non-Significant Risk (NSR) designation from an Institutional Review Board (IRB)

Translational Devices to Treat Pain

Goals

- Translate innovative, effective and non-addictive device-based technologies from pre-clinical studies to clinical trials to treat pain in humans
- Support clinical trials that provide information that cannot be practically obtained through additional non-clinical assessments

Entry Criteria

- Comprehensive supporting data from models representative of the intended patient population
- One or more clinically meaningful outcome measures
- Compelling case for IDE and/or IRB approvals
- *Strongly encouraged* (not required) to consult with the FDA via a Pre-Submission meeting

TDTP Responsive Activities

UG3 / U44 Phase I

- Non-GLP (Good Laboratory Practice) animal studies to develop surgical techniques relevant to the device, define relevant therapeutic parameters, and refine device design in preparation for subsequent GLP testing for regulatory approval
- In vitro and animal testing to meet FDA recognized ISO/ASTM Standards
- Activities to become GMP (Good Manufacturing Practice) compliant
- Activities to bring the development process under Design and Quality Systems Control
- Device, software, and firmware design verification and validation activities
- GLP compliant large animal model safety and/or testing of an implanted device
- Activities to support submission of an investigational device exemption (IDE)

UH3 / U44 Phase II

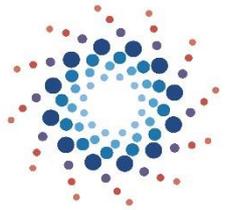
- The UH3 phase will support a small clinical study to answer key questions about the function or final design of a device. Examples of studies that can be proposed during the clinical phase include, but are not limited to:
 - Optimization of the device design with respect to the human functional anatomy
 - Identification of the most simple, reliable, and cost effective device configuration for more advanced clinical trials and eventual market approval
 - Basic proof-of-concept testing in human patients
 - Studies of the key physiological variables that may impact the function of the device in humans
 - Initial assessments of device safety are expected, but only in conjunction with obtaining enabling data about device design or function

TDTP Non-Responsive Activities

Not Responsive

- Animal model development
- Efforts to develop neurotechnology for the study of fundamental functions or physiology
- Delayed-onset studies
- Projects focused on augmentation of neural function in healthy individuals

Small Business Programs



SBIR · STTR
America's Seed Fund

Small Business Innovation Research
Small Business Technology Transfer

- Congressionally mandated set aside
- Broad scope:
 - Therapeutics, diagnostics, tools for research
 - Bench research, translational research, early stage clinical trials
- Multiple Funding Opportunities:
 - A majority of our applications are investigator-initiated and come in through the omnibus solicitations
 - SBIR/STTR set-asides in BRAIN and HEAL Initiatives
- Larger budgets for some topics (e.g. animal or clinical studies)

NIH invites Small Businesses to submit research proposals through the SBIR and STTR Omnibus/Parent Grant Solicitations and HEAL RFAs

Commercialization Support

Pre-SBIR/STTR:

Entrepreneurial Assistance/Training

NIH I-Corps™ (pilot) and C3i Programs

- Open to current awardees of participating NIH Institutes/Centers
- Administrative Supplements: [PA-18-702](#) and [PA-18-517](#)

NIH Applicant Assistance Program (AAP)

- PILOT: [NOT-CA-18-031](#);
www.dawnbreaker.com/aap
- Companies who have not previously won an SBIR/STTR award from NIH
- NCI, NINDS or NHLBI mission
- **Provide free services:** application preparation, needs assessment, etc.

Phase I:

Market Analysis

Niche Assessment Program (NAP)

Entrepreneurial Assistance/Training

NIH I-Corps™ and C3i Programs

Phase II/IIB:

Technical Assistance/Training

Commercialization Accelerator Program (CAP)

Program Staff

Contact Us BEFORE Submission for Advice/Feedback

Cooperative Agreement Mechanisms

*Extremely Clear,
Quantitative and Definitive
Milestones are Essential*

*Annual Go/No-Go Point
at the end of each year*

*Transition occurs via
Administrative Review*



Public Private Partnerships (PPP)

- **Not a requirement**
- **Goal:** to facilitate partnerships between researchers and manufacturers of latest-generation devices
- Template agreements that PIs and manufacturers **can choose to use**
- Relationships were developed as part of the BRAIN Initiative and SPARC Program, but documents / materials / agreements could be used in other programs if the investigators find them of benefit
- If used, a letter of support from the manufacturing partner should be included

BRAIN Initiative

Public Private Partnership (PPP) Program

Facilitate partnerships between investigators and manufacturers

- Companies provide technical support and/or devices
- Pre-negotiated templates for collaborative research agreements
- 4 Industry partners participating in active grants through the BRAIN Initiative Public Private Partnership (PPP)



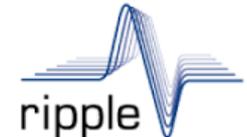
SPARC

Public Private Partnership (PPP) Program



Micro-Leads

NEXEON



Additional company support:

- Engineering: Firmware modification to IPGs, lead prototyping
- Scientific: Company scientists may serve as co-investigators in projects
- Regulatory: Permission to reference device master files at the FDA

SPARC - FDA partnership:

- Facilitates access to regulatory advice and assistance for SPARC awardees

Help us help you

Applicants are very strongly encouraged to:

- Submit Letters of Intent
- Submit draft Specific Aims pages
- *READ THE FOA*

Questions?

1. [Anatomical and Functional Mapping of Pain-Related Visceral Organ Neural Circuitry](#) (U01 CT Optional)
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 - Cooperative Agreements
 - Public Private Partnership